

Case report

An intensive approach to the treatment of disseminated BCG infection in a SCID patient

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Summary:

There is an appreciable mortality associated with BMT in patients with SCID and advanced BCG infection. We present a girl with T-B+ SCID complicated by spina ventosa and disseminated BCG osteitis after receiving a fully matched sibling marrow transplant. Considerable progression characterised by two clinical activations and multiple pleural and perivertebral abscess formations occurred with conventional anti-mycobacterial chemotherapy. She finally recovered with full immune reconstitution after BMT and intensive treatment comprising five conventional and alternative agents that she received for 36 months. No side-effects and/or complications have been seen other than hearing loss.

Bone Marrow Transplantation (2002) 30, 45–47. doi: 10.1038/sj.bmt.1703578

Keywords: allogeneic BMT; SCID; disseminated BCG disease

Case report

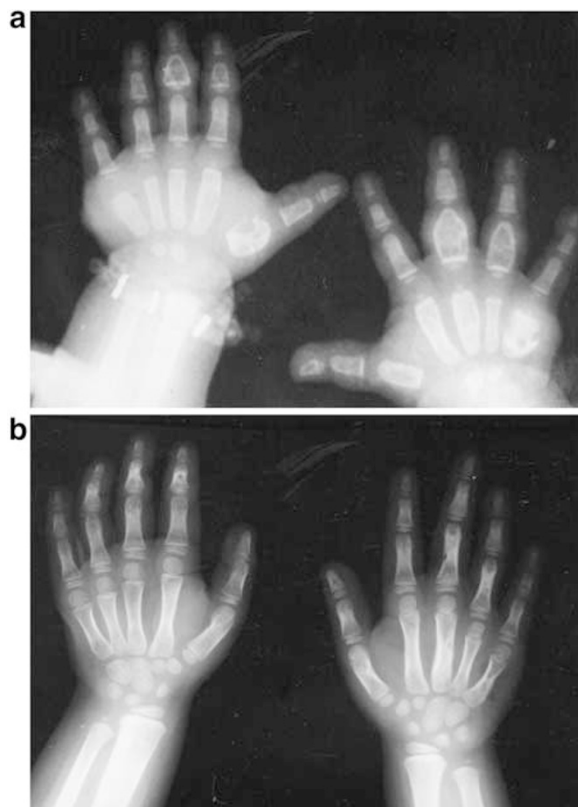
A 6-month-old girl was admitted to our clinic with persistent thrush, diarrhea and cough. Her past medical history was unremarkable other than for a BCG vaccination on her left deltoid muscle during the early neonatal period, according to the standard practice in Turkey. Her symptoms had begun in the first month of life and an 8-month-old female sibling had died with similar symptoms. She was the fourth child of consanguineous parents. Immunological testing revealed T-B+SCID (Table 1). She received a fully matched sibling marrow according to EBMT protocol 1997, 4 weeks after the diagnosis. Standard doses of Isoniazid (INH) were administered prophylactically. Engraftment followed by grade I aGVHD was achieved on day 13. During follow-up, persistent fever occurred for 4 weeks which could not be explained by any viral, bacterial or fungal infection. Subsequently, disseminated BCG infection presented as spina ventosa, hepatosplenomegaly and soft tissue abscess (Figures 1 and 2) and was diagnosed by EZN positive smear, PCR and mycobacterial culture (*Mycobacterium tuberculosis* complex) (Figures 3 and 4). She had received an antimycobacterial chemotherapy regimen comprising four agents (INH 10 mg/kg/day, rifampicin (Rif) 15 mg/kg/day, streptomycin (SM) 40 mg/kg/day, clofazimine 1 mg/kg/day for 2 months followed by just INH and Rif for 4 months to which the organism was sensitive. During this period she did well with full immune reconstitution and both clinical and radiological regression of the tuberculosis infection for 6 months. However, since the BCG disease relapsed in the 6th month of antimycobacterial chemotherapy, she started alternative agents amikasin (Amc) 15 mg/kg/day, ciprofloxacin (Cipro) 30 mg/kg/day, clofazimine 1 mg/kg/day, in addition to two major (INH and Rif) drugs. Amikasin was stopped in the 12th month of therapy when she became afebrile for the second time. She did well, with significant clinical and radiological regression of the tuberculosis infection for another 6 months on anti-tuberculosis chemotherapy (INH + Rif + Cipro + clofazimine). However, as multiple pleural and perivertebral abscesses had been detected at her 18 month follow-up examination, amikasin (short-term) and clar-

The severe combined immunodeficiencies are a group of genetic disorders characterised by profoundly defective T lymphocyte (with or without B lymphocyte) differentiation that leads to early death in the absence of hematopoietic stem cell transplantation.^{1,2} BCG vaccine derived from multiple passages of wild-type *Mycobacterium bovis* is administered throughout the developing world to attenuate the effects of natural tuberculosis infection.^{3,4} However, in individuals with defects of the host immune response, serious BCG infections can occur.^{4,5} We report a patient with SCID who developed disseminated BCG disease after BMT and who improved after successful engraftment in conjunction with intensive, long-term multiagent anti-mycobacterial treatment.

Table 1 Immunological data before and after transplantation

	<i>Before</i>	<i>After</i>							
		<i>2 weeks</i>	<i>2 months</i>	<i>4 months</i>	<i>10 months</i>	<i>12 months</i>	<i>18 months</i>	<i>24 months</i>	<i>36 months</i>
Lymphocyte subsets									
CD3 (%)	20.7	45.1	84.6	73.8	87.0	76.5	69.0	68.0	62.0
($\times 10^9/l$)	0.2	1.0	7.8	3.3	6.8	3.6	2.6	4.0	2.3
CD4 (%)	19.6	8.8	7.8	17	22.0	19	27.0	31.0	31.0
($\times 10^9/l$)	0.1	0.1	0.7	0.7	1.7	0.9	1.0	1.8	1.1
CD8 (%)	0.7	35.7	78.1	60.3	67.0	60.0	45.0	37.0	32.0
($\times 10^9/l$)	0.0	0.7	7.2	2.7	5.2	2.8	1.71	2.2	1.2
CD19 (%)	72.5	42.9	9.5	17.4	9.5	20.5	24.0	28.0	37.0
($\times 10^9/l$)	0.7	0.9	0.8	0.7	0.7	0.9	0.9	1.6	1.4
CD56 (%)	1.7	2.8	4.9	6.6	5.9	5.9	3.8	3.3	4.6
($\times 10^9/l$)	0.0	0.0	0.4	0.2	0.4	0.2	0.1	0.1	0.1
<i>In vitro</i> response									
PHA (%) [n: 65.8 $\pm$ 9.2%]	5.0	NA	NA	31	60	63	57	69	78
<i>In vivo</i> response									
PPD ^a (mm)	—	NA	NA	5	10	NA	NA	NA	NA
Immunoglobulins (mg/dl)									
IgG	83	NA	NA	1509 ^b	1510 ^b	NA	754	NA	621
IgA	105	NA	NA	NA	58	NA	40	NA	26.3
IgM	63	NA	NA	NA	266	NA	69	NA	80

NA = not applied.

^aRecently applied, 12 mm.^bSubstituted.**Figure 1** Bone lesions before and after the treatment.**Figure 2** Fusiform swelling of fingers (dactylitis) and soft tissue abscess.

ythromycin were added to her regimen. At 36 months of treatment most of her bone lesions had improved, the sclerosis and hepatosplenomegaly had regressed and there was no sign of active tuberculosis infection. Antimycobacterial therapy was stopped. Eight months after discontinuation of antimycobacterial treatment, she was thriving normally and still in clinical and radiological remission, although she had hearing loss and required a hearing device.

Discussion

BCG is administered in many developing countries to prevent severe tuberculosis, particularly in children.^{3,4} Complications do occur and the most serious one is disseminated

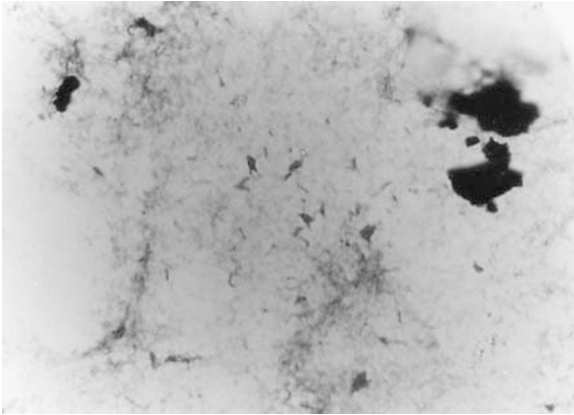


Figure 3 EZN staining of bone of soft tissue biopsy specimen.

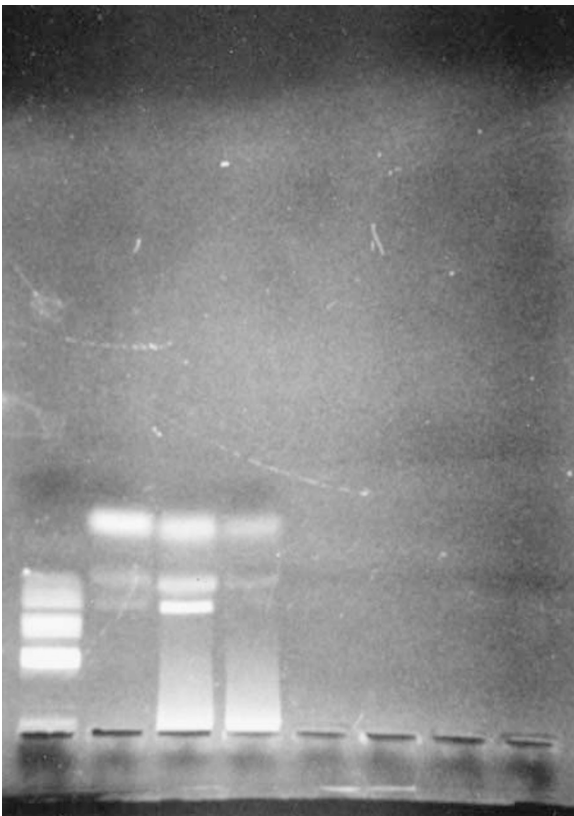


Figure 4 Mycobacterium tuberculosis complex detection at PCR.

disease.³ The estimated incidence of disseminated BCG disease is two cases per one million in vaccinated children.³ However, cellular immune deficiency has been identified as the major risk factor for the disease and a fatal outcome.⁶ Talbot and Perkins,³ by covering a period of 16 years until 1996, reported that immune defects were identified in 24 of the 28 cases (86%) with disseminated BCG disease.

Our case was classified as definite disseminated disease since it met the criteria reported by Talbot and Perkins.³ The child was vaccinated during the neonatal period as a

part of standard practice and remained almost asymptomatic until immune reconstitution appeared following BMT. When she developed fever of unknown origin, the site of the BCG vaccination was initially enlarged and erythematous. However, the fever of unknown origin persisted for several weeks until the fusiform swelling occurred on her fingers and radiological and microbiological examination led us to the final diagnosis. As reported before,⁴ histopathology revealed only a massive disorganised histiocyte response reflecting the compromised immune status and emphasising the difficulty in diagnosing BCG disease in an immune compromised patient.

Two previous reports^{5,7} suggest that early BMT together with appropriate antimicrobials are effective in restoring immunity and curing the infection. Although she had been treated with microorganism-sensitive anti-mycobacterial drugs, she had relapsed twice at 6 and 18 months of treatment, and her disease advanced 18 months later while she was receiving appropriate therapy. We achieved considerable improvement with successful BMT and intensive long-term therapy. It is our belief that successful BMT played the most important role in her recovery. No side-effects and/or complications other than hearing loss have occurred.

We recommend prolonged and aggressive treatment consisting of clofazimine, clarythromycin, ciprofloxacin in addition to the classical agents to cure such cases. Apart from this treatment regimen, anti-mycobacterial prophylaxis should also be intensified in SCID patients before BMT if they have been previously vaccinated with BCG.

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